REMARKS

Pending claims were 1-3, 5-10, and 15-17. All claims stand finally rejected. Applicants respectfully request reconsideration of all rejections in view of the claim cancellation, claim amendments, expert declarations, and remarks below.

Applicants gratefully acknowledge the examiner's withdrawal of prior rejection of claims 1-3, 5-10, and 15-17 under 35 U.S.C. § 112 (2¶) in view of their remarks on July 30, 1996.

REJECTIONS UNDER 35 U.S.C. § 112 (1¶)

All pending claims have been rejected on an allegation of lack of enablement. Applicants traverse these rejections.

1. The examiner avers that it is not clear to her that the rabbit is an art-recognized animal model of Group B meningococcal disease predictive of results in humans.

Applicants have now canceled claim 10, the only claim related to meningococcal disease.

2. The examiner also doubts that the neutropenic rat used by applicants is an art-accepted animal model for the generically-claimed heterologous Gram-negative bacteria and LPS mediated pathology.

The examiner has the initial burden to show that one of ordinary skill in the art would reasonably doubt the asserted utility of the neutropenic rat model. MPEP 2164.07(a)(2). The examiner has cited no reference to support her doubts about the value of the neutropenic rat as a model.

As the examiner no doubt appreciates, applicants' invention is a vaccine and method of use, not an animal model. Given the exemplification of the success of the claimed invention in protecting an animal *in vivo* against bacterial sepsis (see Example 11), and the declaration from expert Steven Opal, M.D. below, the examiner has provided no reasonable basis to doubt the asserted therapeutic value of the inventive vaccine. MPEP 2107.02. As will be detailed below, those skilled in this art recognize the neutropenic rat as the best of the animal models.

Applicants submit for the examiner's consideration a Rule 132 Declaration from infectious disease vaccine expert Steven Opal, M.D., an Associate Professor of Medicine at Brown University, who has extensive experience with the neutropenic rat model for heterologous Gram-negative bacterial infection.

The declarant states that there is no animal model for sepsis other than the neutropenic rat model used by applicants which provides such extensive correlations with human clinical trials. The declarant provides four specific examples of antibodies (HA-IA mAb, anti-lipid A antibody E5, BPI and IL-1ra) for which there is a high correlation between the results with the neutropenic rat and the results with clinical trials with humans.

In addition, declarant describes contractual arrangements with pharmaceutical companies to use the present neutropenic rat model to test their products for potential use in human clinical trials. It is logical to assume that pharmaceutical companies would not take this step if they were not convinced of the usefulness of the neutropenic rat model.

It is clear, therefore, that the neutropenic rat model is art-accepted for the present purposes, and it would therefore be appropriate for the examiner to withdraw these rejections.

3. The examiner refers to Greenman *et al.*, of record, as stating that there is no pharmacotherapy available for Gram-negative sepsis or associated organ failure.

The examiner alleges that Greenman *et al.* teaches that, aside from antibiotic, surgical, and supportive care, no specific pharmacotherapy is available for Gram-negative sepsis or associated organ failure. Current MPEP guidelines make it improper for an examiner to assume that an invention cannot be efficacious merely because of prior failures in the technology. MPEP 2107.02(f).

Further, Greenman actually concludes on page 1101, right column, bridge ¶, that:

> ...[P]atients with gram-negative sepsis who were not in shock experienced a <u>significant improvement</u> in both survival and resolution of organic failures following treatment with E5 anti-endotoxin monoclonal antibody.

Emphasis added.

In addition, in the Conclusions section of the Abstracts, greenman states:

> Treatment with E5 antitoxin antibody appears safe. It reduces mortality and enhances the resolution of organ failure among patients with gram-negative sepsis who are not in shock when treated.

Therefore, Greenman actually supports the type of pharmacotherapy espoused by Applicants.

For these many reasons, the invention as presently claimed is properly enabled, and the examiner is requested to withdraw these rejections.

REJECTIONS UNDER 35 U.S.C. § 102(b)

The examiner asserts that claim 1 is anticipated by Zollinger U.S. patent 4.707,543.

The Zollinger reference has been analyzed by applicant Alan S. Cross, M.D. who is an expert in the field of vaccines against bacterial infections. The analysis appears in the accompanying Declaration from Dr. Cross attesting to the fundamental differences between the present invention and the teachings of Zollinger. These differences are reflected in amended claim 1 which now recites elements of the invention that are fully supported in the present specification and that are not found in Zollinger. As the examiner knows well, to support a rejection of a claim on the basis of a reference, that reference must contain within its four corners all of the elements of the claim. Zollinger does not accomplish, for reasons described below.

1. Zollinger requires that the target bacteria for the vaccine be the same as the bacteria providing the components of the vaccine. See Abstract, lines 4 and 5; column 2, line 26. In sharp contrast, amended claim 1 requires that the target bacteria for the vaccine is not the same as the bacteria providing the components of the vaccine. See Example 10 in which JPDLPS-NMABOMP vaccine was effective against all Gram-negative bacteria tested (Table 5). See also Example 11 in which the J5LGS-NMGBOMP vaccine was effective against *P. aeruginosa*, a bacteria different than the J5 *E. coli* and the *N. meningitidis* Group B from which the vaccine was constructed. Present claims 1 and 6 contain infections by heterologous bacteria as an element of the claims.

2. Zollinger requires that the antibody produced by the vaccine be bacteriocidal. See columns. 2 and 3, legends to Figures 1-7; col. 8, line 14 *et seq.*; column 14, lines 38-68;

column 15, lines 1-60; and, column 15, lines 12-14. In sharp contrast, the claimed vaccine using *E. coli* J5 LPS is <u>not bacteriocidal</u>, as recited in present claim 1.

3. Present claim 1 contains as an element the requirement that the *E coli* used must be the J5 strain that has an LPS devoid of O-oligopolysaccharide side chains; this is not taught by Zollinger.

For these reasons Zollinger cannot be said to anticipate the present claims, and the examiner is urged to withdraw these rejections.

<u>REJECTIONS UNDER 35 U.S.C. § 103</u>

All pending claims are rejected as allegedly obvious over the Zollinger patent of record. Applicants submit that Zollinger does not suggest a vaccine with the elements present in present claim 1 and dependent claims.

For a reference to support a *prima facie* case of obviousness, the examiner is obliged to show by reference to specific evidence in the cited reference that there was (i) a suggestion to make the claimed invention, and (ii) a reasonable expectation that the suggestion would succeed. Both the suggestion and reasonable expectation must be found within the prior art, and not be gleaned from applicants' disclosure. *In re Vaeck*, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991); *In re Dow Chemical Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988).

When an examiner alleges a *prima facie* case of obviousness, such an allegation can be overcome by showing that (i) the allegation is improper (for example, there is a teaching away or no reasonable expectation of success); (ii) objective indicia of patentability exist (for example, unexpected results); or (iii)

secondary considerations exist (for example, commercial success or long felt but unfulfilled need). See, *Graham v. John Deere Co.* 383 U.S. 1, 148 USPQ 459 (1966); *U.S. v. Adams*, 383 U.S. 39, 51-52 (1966); *Gillette Co. v. S.C. Johnson & Son, Inc.*, 16 USPQ2d 1923, 1927 (Fed. Cir. 1990); *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve*, 230 USPQ 416, 419-20 (Fed. Cir. 1986).

Zollinger does not teach or suggest a vaccine in which the LPS is from the unique *E. coli* J5 mutant that is devoid of O-oligosaccharide side chains.

Zollinger teaches away from a vaccine that is effective against heterologous bacteria by teaching a vaccine whose components are derived from and targeted to the same bacterium.

Zollinger teaches away from a vaccine that does not raise a bacteriocidal antibody by teaching only a bacteriocidal antibody.

Zollinger teaches only active immunization and does not suggest passive immunization by the IgG antibody produced by the vaccine of the invention.

Thus, Zollinger teaches away from the structure and function of the claimed vaccine in all critical respects.

For these many and sufficient reasons, Zollinger fails to support a *prima facie* obviousness rejection, and the examiner is urged to withdraw such rejections.

The examiner is respectfully urged to withdraw all rejections and expeditiously pass this application to allowance.

Finally, the examiner asserts that form PTO 1449 did not accompany the references submitted in the IDS dated 01/23/96. A copy of Form PTO-1449 is enclosed.

Respectfully submitted,

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Should additional fees be necessary in connection with the filing of this paper, or if a petition for extension of time is required for timely acceptance of same, the Commissioner is hereby authorized to charge Deposit Account No. 19-0741 for any such fees; and applicant(s) hereby petition for any needed extension of time.